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ABSTRACT

This booklet on marihuana and health begins with general observations made at a press briefing by the Director of the National Institute on Drug Abuse, followed by questions and answers. The last section contains a summary and overview of the Fifth Annual Report to the U.S. Congress from the Secretary of Health, Education, and Welfare. The information in this section includes a discussion of the extent and nature of marihuana use. Next are discussions of the chemistry and characteristics of cannabis, animal research, human effects and health implications, other chronic human effects, and therapeutic aspects of marihuana. (RC)

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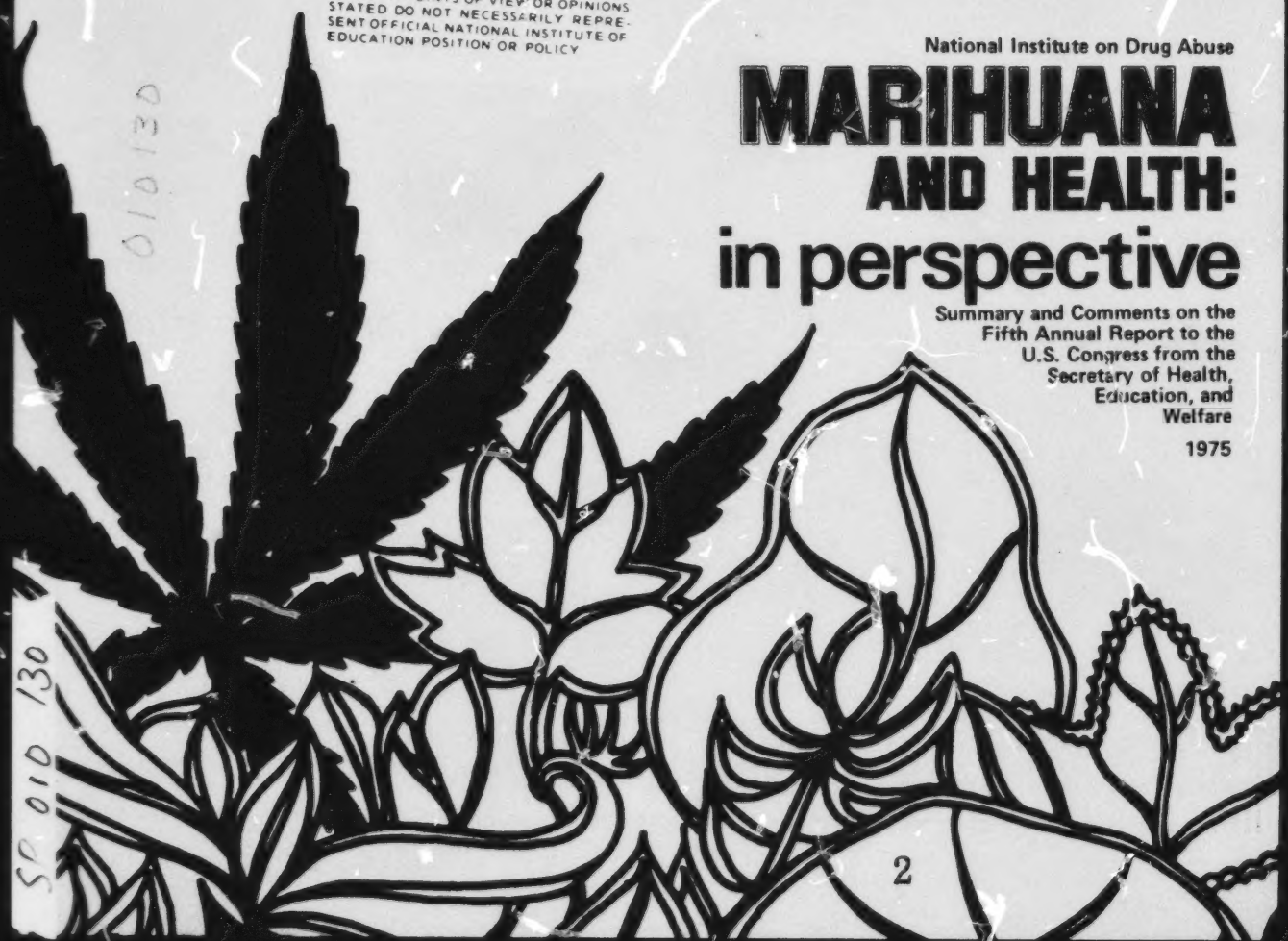

National Institute on Drug Abuse

MARIHUANA AND HEALTH: in perspective

Summary and Comments on the Fifth Annual Report to the U.S. Congress from the Secretary of Health, Education, and Welfare

1975

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Foreword

Marihuana use, an issue once marked by emotionalism, is increasingly being examined thoughtfully. Much has been learned about marihuana use and its personal and social consequences. Yet, much remains to be understood. It is clear that marihuana is not a subject for simplistic analysis.

The current edition of *Marihuana and Health* represents the fifth in a series of annual reports from the Secretary of Health, Education, and Welfare to the Congress as required by Title V of Public Law 91–296. Last year, the fourth report in this series raised fundamental questions about the role of cannabis in altering the body's immune response, endocrine functioning, and basic cell metabolism. Although more data are now available, the direct health implications of these earlier laboratory findings are still not certain.

The *Marihuana and Health* Report does not give marihuana a clean bill of health as some would hope. Nor does it support the fear and irrationality that still characterize some of the public debate about marihuana. Instead, it is a progress report on our effort to understand a challenging health problem with immense social, political, and economic implications.

The Report is limited to a discussion of health issues and does not focus on the related social policy issues of decriminalization and law enforcement. Nevertheless, a discussion of any aspect of marihuana prompts concerns and questions about these broader public policy issues. Therefore, we have included a question and answer section from the *Marihuana and Health* Report press briefing to bring this added dimension to our dialogue. While it is important to understand the relationship between health and public policy concerns, it is essential to keep the health issue separate from decriminalization activities. Decriminalization at the State and local levels should not be interpreted as a signal that marihuana is safe.

So far, the public debate on the health aspects of marihuana has itself been misleading because too much of that discussion focuses only on biological changes resulting from marihuana use and not on the immediate hazards of marihuana intoxication. Although areas of serious concern remain, no convincing evidence has been uncovered to indicate permanent biological harm. On the other hand, the evidence on marihuana intoxication shows that it clearly presents a danger. Even with small dosage levels of marihuana, psychomotor performance is impaired.

Such intoxication can have dangerous consequences in such areas as traffic safety and job performance. Even intellectual performance, and in particular, immediate memory, are also impaired while under the influence of marihuana.

Currently 33.6 million Americans have used marihuana and 13.3 million continue to use it on a regular basis. This should cause all of us to rethink the consequences of increased marihuana use. We hope this summary of the *Marihuana and Health* Report will be useful to that end.

Robert L. DuPont, M.D.
Director
National Institute on Drug Abuse

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Press Briefing: General Observations

In terms of the public's concern about marihuana and the health consequences, the primary concern appears to be: What does marihuana use do to the body? What are the long-term consequences? There are a number of ways that question gets formulated. One of the most major concerns has been the concept of progression from one drug to another—the idea that somehow if a person uses marihuana, he will go on to use other, presumably more dangerous, drugs. We've had some research reported in the last year that is very interesting on this point. And just to make a very brief summary of that: There are clear stages in drug-using behavior, but this progression does not appear to start with marihuana. Marihuana is a link in a chain, or a step in a stairs if you will, and not unique in itself. It appears that young people, as they are going through adolescence, begin their drug consumption with beer and wine. Following that step, there's a next step in two directions; one is to cigarettes and the other is to hard liquor. The next step for both groups, if the young person goes on, is almost inevitably to marihuana use. Many people, of course, stop at any one of these steps, but for those who continue, the next step is to other illicit drugs—most often tranquilizers, amphetamines, and barbiturates. Then—for those who go on—the next step is to LSD and other hallucinogens, followed by the final step in this progression to the use of what are generally known as the hardest drugs, heroin and cocaine. Similarly, it's interesting that as young people or any people are giving up drug use at each of these steps, they tend to go back down the same series of steps in the reverse order. A person who is giving up heroin tends to do that and comes back down the steps to the use of other illicit drugs, including marihuana, hard liquor, and tobacco, to beer and wine. So our earlier assumptions that there were no stages or progression have not been confirmed. It does indeed look like there is a predictable progression.

The second point in this area has to do with the heavy consumption problem. Here I think we have some new data that are of concern. It appears that people who are using marihuana have somewhat more difficulty limiting their consumption than many of us would have thought. [The statistics show that in contrasting frequent marihuana use with alcohol use,] . . . only 9 percent of the people who had used alcohol at all had used it as many as 20 times, whereas among the marihuana users, this figure was 22.5 percent. This means that almost one-fourth of the people who had used marihuana at all had used it about 20 or more times. That's clearly different from the pattern with alcohol. It is much more like the pattern with cigarettes where about two-thirds of those who had used that drug at all reported using it on a daily basis, or the drug heroin where 33 percent who had used it at all reported use on a daily basis. . . . so that the issue of a progression to very heavy use is one that we are concerned about.

Finally, I will just say a word about the marihuana intoxication area. In our preoccupation with looking for long-term permanent health consequences, we have overlooked the fact that the marihuana user, while using the drug and in the immediate hours after using it, does have a performance deficit associated with the intoxication that is not too different in terms of its effect on performance from that produced by alconol. Oftentimes, the

accounts that are carried in the press emphasize the absence of negative health consequences. I am concerned that by this process we reinforce the concept that the marihuana user doesn't have to worry about the intoxication effect. There is clearly a problem here that must be of concern to the individual. Of course, most users understand this in the area of driving, the performance in industrial settings, or any other settings which require attention, adequate motor performance, and intellectual performance. These are temporary changes, but nonetheless they are very important. I reviewed the very high levels of marihuana use, particularly in the youth population, and am very gravely concerned about motor vehicle accidents in that population.

Well, with that as a very brief summary, I'm open to questions.

Press Briefing: Some Questions and Answers

Question:

Dr. DuPont, I would like to frame this question very precisely so that we will both be talking about the same thing. Yesterday, in New York, the American Cancer Society released a survey of the smoking habits of teen-aged women, 15–18, and compared it with 1969. They found that not only are more women and more girls smoking but they are also smoking more. Now, taking into account the way that these two drugs, tobacco and marihuana, are normally used, which is the greater public health menace?

Dr. DuPont:

At the current use levels, obviously cigarette smoking is causing more health problems than marihuana. I think, though, that you point out something that I meant to cover in my presentation. These behaviors are linked so that, in fact, this rise in marihuana use among youth, which I described, has also occurred for cigarettes and alcohol and other drugs. The use levels of these drugs have all advanced as a front, and when they go down, they go down as a front also. We once thought that they behaved like a teeter-totter. For example, if a person were using alcohol, he would not also be using marihuana, and the other way around. This is not the case. People who use alcohol tend to use more marihuana; people who use cigarettes tend to use more marihuana; people who use more marihuana are more likely to smoke cigarettes and use alcohol. That is, all drug-using behaviors are linked.

Question:

Dr. DuPont, what is your position on decriminalizing the use of marihuana? Do you fully agree with that?

Dr. DuPont:

I find the word "decriminalizing" one that confuses communication rather than promotes it. So I am going to do my best to avoid using that word, and instead of using the word, I'll describe the concept. With respect to what penalties are talked about when we talk about lessening, there is room for some difference of opinion—some range of ideas. Let me describe briefly what it is I am talking about. A few years ago, there was a very polar extreme in this country in thinking about penalties for marihuana possession ranging from legalization, that is, making it as available as we make cola or cigarettes in this country, to locking possessors up and throwing away the key on the other extreme. We have progressed a long way since then, and the current debate in the United States is very narrow in terms of what the right penalty ought to be for marihuana possession. If I can state it this way, on the extreme of the hard-line view about this is the use of very short prison sentences. For example, S. 1., the new reform legislation in the Senate now includes, as I understand, up to 30-days imprisonment for

marihuana possession, which is a very light penalty. That now represents one extreme. The other extreme is the policy that has been adopted by a number of States to substitute fines for imprisonment. Personally, my view on this is that we do not need to threaten young people with imprisonment to discourage their use of marihuana, and that we should substitute in place of imprisonment a fine, a monetary fine that signals to the public that we as the Government and as a country are opposed to the use of marihuana, but that we do not consider the possession of small quantities for personal use the kind of problem to be dealt with by putting people in prison. For some people that means decriminalization and for others it doesn't. I know I have been too long on this, but one last point. We talk about six States in the United States that have "decriminalized" marihuana. I call your attention to the fact that two of those States, Ohio and California, continue to use the criminal law but have substituted a fine within the criminal law. This is a very complex distinction for some very high-powered lawyers to start making. The point I want to make that does not require the understanding of a high-powered lawyer is that we want to get away from using prison or the threat of prison for the simple possession of marihuana.

Question:

Can we go over again your views on—I won't call it "decriminalization"—what should be done to someone who is arrested for possession of a small amount of marihuana? And what should not be done?

Dr. DuPont:

Yes. There is now a very broad consensus in the United States that marihuana use should be discouraged and that the Government's role is to discourage marihuana use. But there's a question about how the Government does that. Basically, I think most people agree that it does not make sense to put people in prison for the possession of small amounts of marihuana. To some people, that means "decriminalization." I, myself, support the concept of the use of a civil fine, a noncriminal fine of a modest kind, something in the range of $25.00, to convey the message that marihuana use is prohibited behavior, but also not to threaten the young people with a criminal record or incarceration. There is some variation from State to State on that, but I think it is a position that has very broad support throughout the country.

Question:

Do you think that we are getting closer to seeing this?

Dr. DuPont:

Oh yes, it's happening across the country right now. There are six States that have substituted nonimprisonment penalties, and I think there will be more. The problem is that the word "decriminalization" has gotten to be kind of a buzz word—a scare word—that politicizes people and induces a kind of fighting, contentious attitude. That's probably the biggest problem we have right now. We should step aside from that and ask, What do we really want to do to the person, young or old, who is caught with small amounts of marihuana? What should happen to him? When we get to this question, there is very little feeling that that person ought to go to jail.

Question:

(A question about the consequences of marihuana and alcohol use.)

Dr. DuPont:

This is the thrust of the question about cigarettes. I would say that for all of the drugs we have mentioned there are many people who use them without suffering negative health consequences. For each of the drugs, there is a spectrum of negative health risks that a user takes. Marihuana has some of the negative characteristics of both alcohol and tobacco. That is, it is taken in the lungs, so it has the respiratory irritating effects, including the bronchitis and, potentially, the lung cancer problems associated with cigarettes, plus it has the negative intoxicating effects of alcohol. I'll tell you one difference that is very striking: the overdose potential of alcohol. Alcohol really does kill people from overdoses through respiratory suppression. The public does not understand this, but many people are dying from overdoses of alcohol. Marihuana is not that kind of a drug—in fact, the single most striking characteristic about marihuana is the low toxicity in terms of death. It is virtually impossible to die from an overdose of marihuana. So I would try to avoid comparing the drugs because I don't think we know enough about marihuana. I'm as concerned about the potential danger of marihuana as I am about cigarettes and alcohol. I would say today, at our current use levels and our state of knowledge, that there is no question that alcohol and tobacco are causing us far more health problems than marihuana does. There is no question on that point. The question of the potential and the question of new knowledge leaves open the door to the possibility that consequences of marihuana use will be much more serious than we know now. But on the basis of our present facts, it is clear that those traditional drugs cause more health problems than marihuana does.

Question:

Dr. DuPont, you have an interesting chapter in this book on therapeutic aspects, and you do point out that it is likely that if cannabinoids become standard medicine, they would be synthetics rather than derivatives of the natural thing. But, at any rate, do you see any likelihood in the near future of rescheduling cannabis from schedule 1, which states that there is no therapeutic use, to perhaps schedule 2?

Dr. DuPont:

I can imagine rescheduling cannabis. Yes, that's not inconceivable at all. In fact, one of the things we want to do is to apply the routine standards to cannabis. The Government, in the last few years, has gone through a very great, wrenching crisis around the issue of drug use. One of the things we have done through the Controlled Substances Act is to establish some criteria for handling drugs in a rational fashion. I think it is time to apply the same rational decisionmaking to cannabis and to other drugs that we apply to the more conventional pharmaceutical products. That's a process that I very much support. Now let me describe the therapeutic status of marihuana. It is in an investigational status. While it remains in an investigational status, there is no reason for rescheduling it. I can imagine, in the not too distant future, there being approved uses for products derived from or similar to the products that are in marihuana. When that happens, and I think it probably will, that will be the time, it seems to me, to act in terms of rescheduling. We should treat this not in a scary, politicalized, emotion-laden way but treat it just as we would any other pharmaceutical product. After all, opium is the substance that scares the heck out of most people, and yet we use codeine routinely in the United States. Codeine is a product that is derived from opium; heroin is also derived from opium. We don't

want to use heroin, but codeine we do use. And I think the same kind of evolution will go on with marihuana.

Question:

Dr. DuPont, could you succinctly restate what you were saying about the lethal effects of alcohol and tobacco compared to marihuana?

Dr. DuPont:

We have clear evidence of the lethal effects of alcohol and tobacco--alcohol through the overdose effects as well as obviously through intoxication. The overdose effect I'm talking about occurs when people take so much alcohol that their respiratory center is suppressed and they die of the overdose. We do not have any similar evidence for marihuana. In fact, we know that marihuana is not a drug that is susceptible to causing death even in extreme situations. One of the most striking characteristics of marihuana is its freedom from this kind of lethal toxicity.

Question:

Dr. DuPont, the United States Government and society are perfectly happy to allow people to make the decision for themselves with regard to alcohol and tobacco. We know that it is bad for us—we are told that it is bad for us. Why this terrible resistance to something that you've just said we know is not as lethal as tobacco and alcohol?

Dr. DuPont:

Well, it is a great wonder to me how we approach the issue of safety in this recreational drug field. The argument generally goes something like this: If everyone who uses it doesn't keel over, then we must let people make individual decisions. Let me show you another area that is related to that but to which we apply a totally different scale. That's in the pharmaceutical area. We are talking about drugs that are used by the American public. If we find a negative health consequence to a pharmaceutical substance such as the antibiotic, chloramphenicol, a useful antibiotic which produces negative consequences in 1 per 10,000 cases, the drug is removed from the market. For example, there is an argument right now about removing birth control pills from the market because they produce thromboembolism in 1 or 2 or 3 in 10,000 cases. We're not talking about giving people the right to decide individually whether they use these drugs; we're talking literally about taking the drugs off the market. And, yet, here in this other area, we've got a whole different view of the issue of safety. Now I don't know how to put those two things together, but there's obviously something to be said for thinking about risks. Just because we allow people to take risks with one substance, or several substances, is not a very good argument to have more of that go on. On the other hand, it is a good argument for not putting people in jail. I think we can deal with chloramphenicol or with birth control pills without putting the users in prison! And I think that similar kinds of regulatory approaches make a lot of sense for cannabis and for alcohol and tobacco.

Question:

Dr. DuPont, what kind of ammunition does this report give to a parent of a teenaged child to discourage him from consuming marihuana for purely health reasons if the use is recreational, infrequent, not taken before an

examination, or while driving. What ammunition does this still give to the parent of that teenager to discourage the use, and if you were the parent of the teenager and your child came home and said, "I'm going to take one of the three—booze, cigarettes, or marihuana," which one would you choose for your child?

Dr. DuPont:

Well, I think that a parent in relating to a child really has to approach the drug problem as a whole and not pick out any particular drug. One should recognize the fact that the child is going to be exposed to a wide variety of substances, both legal and illegal, and that many children will use a variety of these substances. I think it's important for the parent not to get so terribly uptight about whether the child does or does not use any particular drug once or twice, or even a number of times, recreationally. This is certainly the approach I have to my children, although they are a little young for that, the oldest being 10. The parent should talk with the young person about the consequences of the decisions that he or she is making, and will have to make, in the context of his adolescence. And personally, my advice with respect to any of these substances—if you are not using them—I would recommend that you not begin. Drug use is expensive, it's messy, it's of very limited value in terms of the person's lifestyle, and there are serious health risks associated with all the drugs. On the other hand, I think that if a person does decide to use them, and this applies to my children or myself or anyone in my family, I would say to use as little as possible and as responsibly as possible. Now with respect to my family and all of us, unfortunately everybody does not have the ability to control their consumption of these drugs the way they would like. This is the point I was making about marihuana earlier, about the likelihood of going on to heavy use. The same thing is true of alcohol, as many of you know. Not all people can control their consumption of alcohol. Before they start using alcohol, there is no way for them to know that it can have a very disastrous effect—they may be one of those who cannot control their consumption. So I would say that this is one of the things that I'm concerned about. If a young person does use any of these drugs, then I want to help him in a nonhysterical, nonscary way, to use them responsibly. I would encourage him to use less of them. But that, I think, is an individual matter. I think we have got to get into that frame of mind and out of the hysterical-scare approach. Rather than seeing things as extreme, I've heard people say, "Well, if my child used one marihuana cigarette, I'd throw him out of the house." I think that's ridiculous. If a parent thinks a little about that, he would appreciate how ridiculous that approach is. Parents of teenaged children are not unfamiliar with these kinds of problems, not that they like them, but they can't avoid them. The same kinds of issues come up about work, about sexuality, about friends. They are all very complex issues for a young person who is deciding who he is and how he is going to conduct his life.

Question:

(Question about young people's attitudes toward drug penalties.)

Dr. DuPont:

Well, I wish I had the study with me about this, but I don't. One of the things that you find, even in young people, is the remarkable polarization on these subjects with amazing percentages favoring relatively harsh penalties for users of these drugs. I've never quite understood that, but the polarization that goes on in American society is not just limited to older people but

goes on in youth as well. Obviously, the users tend to have a much more lenient attitude than nonusers on the question of penalties for use. I can get you some statistics; I don't have them with me. We have very good data on precisely what the public attitudes are in various age segments toward the issues of legality and drug-using behavior. I think, though, one point that may need emphasizing is that there is a tendency to get very discouraged about the news of the continual rises in drug use; for example, the recent news of women smoking more cigarettes, and the marihuana use data for youth. There is another side to that. A lot of young people are coming to a more sophisticated view of what drugs are and what their lives are all about than ever before. In the long run, this is going to be a very positive evolution for our society. It will be good for all of us to think a lot more soberly about all of our drug consumption. We must not compartmentalize it into "our" drugs and "their" drugs.

MARIHUANA AND HEALTH, 1975: SUMMARY AND OVERVIEW

EXTENT AND NATURE OF USE

Present evidence indicates that cannabis use has significantly increased among Americans during the last two years.

Throughout most of its history American marihuana use has consistently involved a minority of any national age group; however, the most recent national survey data indicate that in the 18-25 age group a majority (53%) have now tried the drug, up from 48% in 1972. Among those surveyed under 18, nearly one in four (23%) has ever tried marihuana — an increase from the one in seven (14%) who reported in the 1972 survey ever having done so.

Current use -- defined as use within the past month preceding the survey -- has also significantly increased among those under 18. Seven percent reported such use in 1972, 12% did so in the most recent survey. There does not appear to have been a similar increase in such use among those over 18 — among whom current use has remained the same or has slightly diminished depending on age, since 1972.

When questioned regarding their plans for future use, one third of those who have used marihuana indicate they definitely intend to do so again. Another third of this group indicate they might do so. Slightly smaller numbers of adults than of youths indicated their intention to continue use (1-1).

While there has been an increase in use by high school and junior high school age groups (attested to by both local and national survey results), future trends of marihuana use in America continue to be uncertain. Despite the other increases noted, use among adults has not increased. In part, this may be explained by research reported in the fourth Marihuana and Health report: changes such as marriage, parenthood and the assumption of other adult roles are inimical to continued marihuana use.

Support for the above interpretations is also found in data garnered from research conducted on a national sample of 20-30 year old men. This nationwide survey found that even within this restricted age group, larger proportions of the men in the younger subgroups used marihuana than did those who were older. Men pursuing more conventional life styles in that they were married and employed full time, were considerably less likely to be using marihuana than were either the unmarried or the unemployed (1-23).

Although there is good evidence of a continuing increase in marihuana use among younger people, there is little indication that such use has come to involve a significant proportion of the older population. For example, if we examine the behavior of those ages 26-34, in contrast to the 18-25 age group less than one third (29%) have ever used marihuana compared to over half (53%) of the younger group. One in four of the 18-25 group had, in fact, used in the month preceding the survey but less than one in twelve (8%) of those 26-34 had done so. In still older age groups use is even less common. Only 7% of those between 35-49 have ever used and only 2% of those over 50 have ever done so. Less than one in one hundred of the over 35 group had used during the month prior to the interview (1-1).

Despite the indications that marihuana has not become popular with older groups and the evidence that its use may be diminished as adult roles are adopted, any prediction regarding the future of cannabis in American society must be hedged with caution. A Gallup poll conducted in 1967 among college students indicated that only one in twenty had ever used the substance, but by 1974 over half (55%) reported use in the Gallup survey (1-9). In seven years, what was once clearly statistically deviant behavior has become the norm for this age group. While in previous years use was correlated with level of education, the percentage now reporting marihuana use is virtually identical for high school drop-outs, high school graduates and college graduates in similar age ranges.

National trends and use patterns mask distinctly different patterns in particular communities or geographical areas. In one Northern California county in which a survey of junior and senior high school students has been conducted each year since 1968, even the earliest findings indicated over one quarter of the ninth grade males (27%) had had some experience with marihuana during the previous year. Among male seniors nearly half (45%) reported use in the year preceding. Current (1975) comparable figures are now 49% for ninth graders and 64% for senior boys. However, the percentage reporting use on 50 or more occasions in the previous year has not markedly increased for the past five consecutive years (1971-1975) (1-4).

During the past five years since the first Marihuana and Health report, cannabis use in the United States has changed in character. Originally marihuana's popularity was concentrated among young people associated with a "counter culture." It was regarded as symbolic of their opposition to traditional values and to the prevailing political climate (Cf. the first Report, 1971).

*Numbers in parentheses refer to the several technical chapters and their lists of references. Thus, 1-1 refers to reference one in Chapter 1. This is the specific study from which the data are abstracted.

As use has spread to involve larger numbers and to more conservative segments -- it has now been experienced by a majority in many groups -- it has lost some of its nontraditional, antiestablishment symbolism. Early use often involved opposition to more traditional alcohol use. Now those who use marihuana are also very likely to use alcohol -- frequently simultaneously. Marihuana use seems unlikely to displace more traditional alcohol use even among the young. Continuing research on patterns of multiple drug use and drug using contingencies may better enable us to predict both individual and group drug use.

Use patterns in other countries, even those in which cannabis use has been endemic for many years, provide few clues to future use in the United States. In other countries use is typically class related with the lower classes, the traditional users. While in some of these countries of traditional use there are now middle or upper class users, such users seem to have adopted marihuana as part of an international youth culture rather than by diffusion from native users. Expectations with respect to drug effects also differ in that traditional users do not share the recreational orientation that characterizes American users.

CHEMISTRY AND CHARACTERISTICS OF CANNABIS

Although a detailed discussion of developments in cannabinoid chemistry is of primary interest to the specialist, there is a range of developments of more general interest. The plant, cannabis sativa, far from being a simple substance is, in fact, chemically quite complex. The last several years of research have resulted in an increasingly sophisticated knowledge about this complex substance. There is a growing awareness of the need to much more adequately describe several major cannabis constituents if we are to adequately specify the nature of the material. The United Nations has now recommended that all research reports on cannabis describe not only the amount of delta-9-tetrahydrocannabinol (the major psychoactive ingredient) but that of cannabidiol and cannabinol as well.

The ability to synthesize various chemical components of marihuana as well as the drug's metabolites (i.e., compounds resulting from the biological transformation of the originally ingested material) is a significant advance. Availability of such pure substances provides researchers with necessary materials for careful study of the physiological role of marihuana's various components.

While primary interest has tended to center on delta-9-THC because of its role as the principal psychoactive ingredient in cannabis, the part played by several other ingredients may be important in producing other cannabis effects. These other ingredients alone or in combination, may account for possible adverse health consequences or contribute to the possible therapeutic usefulness of the drug.

The detection and analysis of marihuana in body contents such as blood, saliva, urine and breath is a problem important both to basic research and to forensic medical applications. For research, it is important to develop methods that accurately determine how much smoked or otherwise ingested marihuana actually becomes physiologically available. These amounts may be substantially different than the amount ingested because of losses that occur in consuming marihuana, delayed bodily absorption, and individual differences in ability to metabolize the drug.

In the clinical setting, appropriate treatment of the unconscious patient brought to the Emergency Room following an accident may be dependent on knowing whether he or she is marihuana intoxicated. In other medical situations being able to determine with certainty the level or fact of being intoxicated may make the diagnosis of the patient much easier.

The general increase in marihuana use has undoubtedly brought with it an increase in the numbers who drive while cannabis intoxicated. Recent evidence (Cf. Driving Effects) further confirms cannabis adversely affects driving. Thus, there is a real need for the development of one or more roadside methods that can be rapidly employed in much the same way as current tests for alcohol intoxication.

Although simple, rapid detection methods are badly needed, detecting marihuana use is inherently much more difficult than detecting alcohol use. The quantities of drug involved are much smaller and they are very rapidly transformed into metabolites which differ chemically from the originally consumed material. As with alcohol, it is important to quantify the level of use for all of the purposes outlined. During the past year considerable progress has been made in improving detection techniques.

In addition to newer, thin layer chromatography and high pressure liquid chromatography methods, two other techniques have shown unusual promise. Radioimmunoassay (RIA) is a technique in which an antibody specific to a drug or its metabolites is developed and then "tagged" by means of a radioactive molecule in its structure. When a solution of the tagged antibodies and of the body fluid in which the drug to be detected is made, the radioactive markers are displaced proportionately to the drug quantity present. The accuracy of RIA is now being compared with that of more cumbersome procedures.

A second technique under development is called the enzyme multiplied immunoassay test, or EMIT. The antibody reaction which is its basis is similar to that used in the radioimmunosassay technique. EMIT has the added advantages of involving less work, less sophisticated equipment and is more rapid thus making it more suitable for

rapid screening. Field trials on EMIT are ongoing.

A third method which also shows promise of shortly becoming available is likely to be most useful for traffic safety purposes. It utilizes breath samples in a manner roughly analogous to present roadside alcohol intoxication detection.

As has been repeatedly emphasized, marihuana and hashish vary widely in THC content and thus in their ability to intoxicate. This variability results from differences in plant genetic origin, conditions of cultivation and preparation of the material including the degree of concentration of leaves and flowering tops. A relatively recent addition to the illicit market is hashish oil, a substance having a THC concentration of 40-50% as compared to the 1-2% THC content of most marihuana ordinarily available in the United States. Increasing availability of such more potent cannabis preparations may have quite different implications from the more commonly used, weaker preparations that have been available in the past. Use of stronger material, particularly by relatively naive users unaccustomed to its effects, is considerably more likely to result in acute panic and other adverse reactions. Stronger cannabis and cannabis derivatives used under conditions in which the dose is more difficult to control, may also result in marked impairment in driving or other complex psychomotor skills. Such unexpected effects could have serious implications.

ANIMAL RESEARCH

A wide range of research on the effects of marihuana has been conducted with animals because their genetic and learning histories, unlike those of humans, can be accurately specified. Animal models also permit the use of high doses and other procedures not possible in human research. Apart from studies of various physiological effects of the drug which have been discussed primarily in relation to human findings, there are some behavioral observations in animals that are of interest.

Because there has been some question about the role of marihuana as a possible releaser of aggression, studies of animal aggression following marihuana or THC administration have been done. Generally, these drugs have been consistently found to suppress aggression when the animals are not under stress. When animals are stressed by a variety of means (e.g., food deprivation, sleep deprivation, morphine withdrawal, etc.) THC or marihuana tends to increase aggression.

The results of behavioral studies in animals suggest that the effects of cannabis on aggression may be complexly related to the degree to which the animal is subject to stress and the length of time over which it has received the drug. The degree to which these observations are relevant to human behavior is unknown although they do provide a basis for devising related human studies.

In an experiment which studied monkeys in three to six member social groups several changes of interest were found. Given oral doses equivalent to very heavy human cannabis use, the monkeys responded much like humans. They slept and rested more frequently; active social interaction such as grooming of others was reduced. Over more extended periods of administration, the monkeys gradually showed less and less of these effects. While aggression was initially reduced, after receiving THC for weeks or months during the year-long study the monkeys became irritable and aggressive (hitting, biting, chasing behavior increased). There was no evidence of the reduction in testosterone levels that has been reported in humans nor were menstrual cycles of females apparently disturbed (4-67).

More detailed discussion of the extensive research that has been done with animals is to be found in the technical chapters of this report.

HUMAN EFFECTS AND HEALTH IMPLICATIONS

Effects of marihuana can conveniently be divided into: 1) the acute effects of cannabis intoxication and 2) the longer range consequences of regular or chronic use. It is considerably easier to study acute effects and so after eight years of intensive investigations many, if not most, of these effects have been elucidated.

Human Acute Physiological Effects

An increase in heart rate and a reddening of the eyes have been the most consistently reported physiological effects of marihuana. Heart rate increases are closely dose related. Early awareness of this marihuana-induced tachycardia created concern over possible adverse cardiovascular effects of the drug especially in those with coronary disease. Several reports issued in the past year have confirmed a preliminary finding from last year. Marihuana use decreases exercise tolerance prior to the onset of chest pain (angina) in those with heart disease (7-137, 3, 4). Use by those with already existing cardiovascular deficiencies, therefore, appears to be unwise. The contrasting finding that marihuana produces minimal changes in heart function (aside from a rate increase) in young, healthy men illustrates that the drug's effects may significantly differ in persons with pre-existing medical problems from those in normals.

A number of reports have confirmed and extended initial evidence that smoked marihuana when acutely administered, results in improved pulmonary function as measured by bronchodilation (7-156, 157, 158). Optimism created by this finding has since been tempered by evidence that under conditions of more chronic use pulmonary function is impaired, rather than enhanced (7-62).

Evidence that marihuana and especially its principal psychoactive ingredient, delta-9-THC, are effective in reducing intraocular pressure in both normals and in glaucoma patients has been further confirmed. While some question exists whether this effect is due to a nonspecific drug-induced relaxation shared with other sedative drugs or to a more specific marihuana reaction, more recent evidence suggests it is THC-specific (Cf. Therapeutic Aspects).

Understanding of the metabolism and the mechanisms of action responsible for various marihuana effects has increased although many questions remain open.

More sophisticated attempts to measure various aspects of psychological and psychomotor performance have been generally consonant with subjective reports. Impaired memory, altered time sense and performance decrements on a variety of tasks have been experimentally confirmed. Generally, the more complex the task, the greater the degree of disruption produced by acute intoxication. Tasks which are relatively simple and with which the person is familiar are minimally affected. As the task becomes more demanding and novel and/or the dose of drug increases, performance decrements become larger. At lower doses, evidence confirms users' assertions that they are often able to "suppress the marihuana high" when the situations so demand.

Although users have reported enhanced auditory, visual and tactual awareness and sensitivity, experimental research has not confirmed these reports.

Driver Performance and Traffic Safety

Because of the prominent role the automobile plays in our society, the possible implications of marihuana intoxication for traffic safety have been emphasized. Early reports were more optimistic about driver performance than recent evidence. Those consuming alcohol to the level of legal intoxication were originally found to make significantly more driving errors in a driving simulator situation than those who had consumed a "social dose" of marihuana. While the marihuana-intoxicated subjects indicated that their driving performance was affected, they felt they could compensate by driving more slowly and cautiously.

Present evidence, whether derived from driver test course performance, from actual traffic conditions or from the experimental study of components of the driving task, all indicates that driving under the influence of marihuana is hazardous (7-90). The increasing simultaneous use of both alcohol and marihuana by drivers poses a threat that may well exceed that of either substance alone. While the parameters of risk connected with the use of marihuana alone or in combination with alcohol prior to driving are not yet known, discouragement of such use appears justified. A more accurate determination of the extent of risk involved in the various levels of intoxication would be desirable. Such studies are complicated by individual differences but are by no means impossible to execute.

Although there has been little systematic study of the relationship of marihuana smoking to possible pilot error, evidence related to driving is at least partially germane. Such skills as detection of peripheral stimuli and complex psychomotor coordination involved in driving are probably equally important in flying. In fact, the inherently greater complexity of flying suggests that performance is even more likely to be impaired under conditions of marihuana intoxication than is driving. Only one preliminary report of pilot performance has appeared in the research literature. This report indicates that under flight simulator test conditions experienced pilots show marked deterioration in their performance while marihuana intoxicated (7-108). More detailed studies are planned to better understand the nature of the performance deficits produced and their duration. A danger common to both driving and flying is that some perceptual or other deficits may persist for some time beyond the period of subjective intoxication. Under such circumstances an individual may attempt to fly or drive without realizing that his functioning is still impaired although he no longer feels "high."

Chronic Use--Special Problem Areas

Last year's report singled out several special problem areas involving potentially serious adverse consequences of chronic cannabis use. Subsequent research has not definitively resolved the questions raised but has expanded our knowledge base.

Some apparent inconsistencies in research findings regarding reduced plasma levels of the male hormone, testosterone, may be explained by the differing length of time users had been smoking before such levels were assessed. For example, the findings of one study that did not show a decrease during a several week period were matched by those in another study in which there were early negative findings. However, after four weeks elapsed a definite drop occurred (7-100). The decreases that have been found have still been within what are generally conceded to be normal limits. Their biological significance remains in considerable doubt. A preliminary finding that a marked reduction of sperm count (58%) occurred in five cannabis smokers following controlled conditions of smoking has been reported (7-171). While this poses the possibility of diminished fertility in chronic users, the small size of the sample and the study's preliminary nature make the work inconclusive.

With regard to hormonal aspects, two other adverse effects remain possibilities: 1) Inter-

ference with normal growth and sexual development of adolescent heavy users and, 2) Abnormal sexual differentiation of the male fetus developing in a mother who heavily uses marihuana during early pregnancy. No actual evidence for either of these speculative possibilities has yet appeared in the scientific literature.

The question of a cannabis induced impairment of the body's immune response remains important because of its potentially far reaching clinical implications. While a number of investigators have published findings that suggest that marihuana may interfere with cell-mediated immunity, other investigators have not found such evidence. Some of these differences may reflect procedural variations; nevertheless, the clinical significance of the positive findings remains in considerable doubt. At least one study of experienced marihuana smokers under well-controlled, closed experimental ward conditions found initial evidence of impaired immunity upon their admission to the study. However, by the 63rd day of controlled cannabis administration, their immune response had apparently returned to normal (8-39). This finding suggests that the impairment of immunity initially detected in these and other marihuana smokers may be related to factors other than marihuana use.

The implications of laboratory findings of inhibition of DNA, RNA and protein synthesis, all basically related to cellular reproduction and metabolism, are at present unknown. These findings based on in vitro (outside the body) study of animal and human tissue cultures are also being followed up and extended.

Similarly, no conclusive evidence exists regarding damage to human genetic functioning (i.e., chromosomal damage produced by marihuana). While the most carefully controlled studies have failed to demonstrate such damage, the research to date must be regarded as insufficient to permit definitive conclusions.

Presently, preliminary evidence of a range of potentially serious consequences of marihuana use exists. As indicated, these include: Disruption of basic cell metabolism through interference with DNA and RNA synthesis, possible interference with pituitary function, in turn, affecting testosterone production and possibly having other endocrine effects and interference with the body's disease defenses by affecting the immune response. Despite this laboratory evidence, the clinical implications remain in doubt. While no evidence has appeared indicating that marihuana users here or abroad suffer from unusually high rates of infectious disease or cancer which might result from defects in the immune response, carefully controlled large scale clinical studies have not yet been conducted. Similarly, there is no evidence — but neither have there been adequate systematic studies -- to establish whether users have significantly lower fertility rates or more serious problems with impotence than non-users.

The failure to detect gross clinical findings that might be expected does not, of course, mean that these issues have been resolved. To date systematic studies of matched samples have been modest in size. Detection of rarer consequences of use is less likely in studies of limited size and extent. As the number of chronically using Americans increases, larger scale epidemiological studies are becoming feasible. Plans for such studies are underway.

OTHER CHRONIC HUMAN EFFECTS

Tolerance and Dependence

Tolerance to cannabis -- diminished response to a given repeated drug dose — has been substantiated by research evidence. Development of tolerance to marihuana's effects was originally suspected because of the obvious ability of cannabis users overseas to ingest larger quantities of the drug without disruptive effects than was possible for less experienced American users. Systematic, controlled studies in which known doses of marihuana or THC were administered over extended periods have now confirmed this (8-53, 80, 109, 111).

The meaning of cannabis dependence is often somewhat vague. If we define it as a physical dependency manifested by physical symptoms following drug withdrawal, there is now evidence that it can occur. The symptoms that have been reported following discontinuance of high dose chronic administration of delta-9-THC include: Irritability, restlessness, decreased appetite, sleep disturbance, sweating, tremor, nausea, vomiting and diarrhea (8-80). It should be noted, however, that the after effects reported followed unusually high doses of orally administered THC under research ward conditions. Such changes have not commonly been observed in other studies nor has a "withdrawal syndrome" typically been found among users here or abroad.

Psychopathological and Neurological Aspects

The question of possible prolonged behavioral effects of chronic cannabis usage has been an area of fundamental concern throughout the American cannabis research program. As indicated in earlier reports, foreign observers have argued that a range of such effects occurs, including a specific cannabis psychosis, diminished intellectual performance and an "amotivational syndrome" (characterized by a loss of interest in work and other conventional activity). Interpretation of such reports has unfortunately been complicated by the lack of adequate control groups, poor research design, use of opium and other drugs, poor diagnostic criteria, nutritional deficiencies and other differing factors of life style.

Even when a particular consequence is correlated with marihuana use, it is often erroneously attributed to the drug use. A recent study of 38 first admissions to a psychiatric hospital illustrates the problem of interpretation involved: While there was a correlation between marihuana and subsequent psychiatric illness, it was less than with such causally unrelated variables as having danced and having drunk beer (7-2).

The acute panic anxiety reaction, previously mentioned in the discussion of acute effects, is probably the most common adverse reaction. However, a more prolonged cannabis psychosis has been reported in Eastern literature. It appears to occur under conditions of unusually heavy use or as a result of ingesting a larger amount than usual. Descriptions do not always distinguish between an acute brain syndrome or toxic delirium marked by clouded mental processes, disorientation, confusion and marked memory impairment and a more prolonged psychotic reaction precipitated by cannabis use. Often it is difficult to isolate the causative role of marihuana from that of pre-existing psychopathology or other drug use (7-64, 112).

Three NIDA-supported research studies of heavy chronic users conducted in Jamaica, Greece and Costa Rica have failed to detect evidence for a cannabis psychosis. However, given the comparative rarity of this syndrome and the small sample sizes used, it is possible that such a consequence was missed.

Studies of college student performance have generally failed to prove evidence of impaired intellectual performance related to marihuana use.

While there was no evidence of differences in grade point average or in educational achievement, marihuana users in one major study had greater difficulties than non-users in deciding career goals and were more likely to have dropped out of college to reassess their goals (7-11). Some of these studies suffer from several shortcomings, however; the samples studied may not have adequately emphasized college drop-outs thus excluding the very group that might have been most adversely affected by heavy use. A second consideration is that students typically have higher levels of ability than the general population. Particularly in more competitive academic environments, they may have above average motivation allowing them to better compensate for cannabis effects. Finally, even moderately heavy American student users use the drug less frequently, in less potent forms and in lesser quantity than more heavily using overseas populations.

Assessing the psychosocial effects of marihuana use in chronically using populations can be complicated. Changes in values and behavior attributed to marihuana use may, in fact, have preceded use rather than the use affecting the change in values. Especially in earlier years, users were much more likely to hold counterculture, antiestablishment views. For these users marihuana had symbolic value as a means of indicating their disdain for the prevailing value system. This disdain was frequently accompanied by a rejection of the traditional work ethic with its emphasis on competitive achievement. The group dynamics of marihuana use may, however, reinforce these counterculture views of more conventional motivation rather than result from any pharmacological action of the drug itself.

Similarly, attempts to create experimental models for testing the existence of such an "amotivational syndrome" have had serious limitations. Tasks chosen as tests may significantly depart from more realistic work tasks; the artificial environment of the research setting may not provide more typical motivational conditions. Two studies involving marihuana administration coupled with monetary reward for work performance did find a decline in productivity with heavier marihuana consumption. In one the task was simple and relatively undemanding, involving repetitive button pushing that could be carried on simultaneously with other activity (7-111). In the other, a more typical work task -- the making of wooden stools -- was carried on (7-13). The distinction between a direct effect on performance as a result of marihuana and on performance as a result of a decline in motivation is not easily made, however. In a third, quite limited study of agricultural performance undertaken in connection with the Jamaican study of chronic users, researchers found some decline in work performance although the decline was not dramatic (7-141).

When one turns to the neurological evidence there is little question that there are acute effects of marihuana intoxication although these are not easily distinguished from those of other psychoactive drugs as measured by conventional electroencephalograms. The EEG changes resulting from electrodes implanted deeply in the brain are dissimilar to other psychoactive drugs (7-67). The behavioral significance of the EEG changes that have been found in chronically using monkeys and in very limited human studies is not presently known.

Work in Greece has not supported previously cited evidence suggesting that brain damage marked by enlarged ventricles may result from marihuana use. The Grecian study, using non-invasive echo-encephalographic techniques for measurement of ventricle enlargement, found no evidence of such brain damage in heavily hashish using men matched with non-using controls (7-49).

Field Studies of Chronic Users

Although other portions of this and previous reports touch on one or another of the three Federally sponsored studies of chronic marihuana use in Jamaica, Greece and Costa Rica, it may be useful to summarize their findings, strengths and weaknesses here. The Jamaican study has been extensively reported in previous Marihuana and

Health reports, a recently published book and in the research literature (7-141). A report on the Greek study was delayed in order to make the data base as complete as possible. The third study in Costa Rica was just completed; its detailed findings will be released by Spring, 1976. In each of these research efforts, an attempt was made to match drug-using subjects with appropriate non-using counterparts. In the Jamaican and Costa Rican projects rather careful matching was done; in the Greek study such matching was less possible. All subjects were males because male use predominates in the cultures studied. Numbers of subjects were necessarily limited by the detailed procedures followed (Jamaica: 30 experimental, 30 control; Greece: 47 experimental, 40 control; Costa Rica: 40 experimental, 40 control, although 80 and 140 users and non-users respectively were actually examined).

The Jamaican study found few physiological or psychological differences between the matched smoker nonsmoker populations. A rather extensive battery of tests of physical and psychological functioning found no differences that could be directly attributed to marihuana use as such. While an attempt was also made to assess chromosomal abnormalities, that portion of the study must be regarded as inconclusive because of technical deficiencies in the methodology for that phase of the project.

The Greek study arose from a clinical impression by Greek observers that Greek hashish users, because of their heavy use patterns and already estaolished researcher-subject rapport, would make a good study population for examining the effects of unusually heavy cannabis use.

A variety of neurological, psychological and physical measures found few changes attributable to cannabis use. Heavy emphasis was placed on possible brain damage as measured by electroencephalographic, echo-encephalographic (Cf. preceding section) and psychological test procedures. None of these measures showed evidence of brain damage (7-49).

The most recent Costa Rican study also examined matched samples of users and non-users especially carefully matched on such variables as age, marital status, education, tobacco smoking and alcohol use. Emphasis was placed on extensive medical examinations with special attention to pulmonary and neuropsychological functioning. Although detailed results have not yet been published, no evidence for a greater incidence of disease or of psychological deterioration has been found in the cannabis-using group (7-23).

None of the three studies found evidence of increased psychopathology or of an amotivational syndrome stemming from the use of cannabis.

While results of these studies must be regarded as somewhat reassuring of the lack of grossly adverse consequences of marihuana use, they can not, of course, be regarded as conclusive for several reasons. All three studies involve relatively small numbers of subjects. Equally limited studies of cigarette smoking, for example, which is known to have serious adverse health consequences, would not have been likely to detect those consequences. Psychological testing techniques are less apt to be satisfactory when used with subjects markedly different from the original standardization samples. To the extent that they are not culture free, performance for both experimental and control groups in cultures unlike those on which they were standardized may both show a culturally derived deficit. This deficit may mask a drug-related deficit in performance. Thus, the tests used may not be sufficiently sensitive to detect a difference that may in fact exist. Finally, it may be argued that the demands of a less technologically oriented society are less complex than those of the industrialized United States. Thus, the failure to find a drug-related decrement in social or work performance may reflect an unimpaired ability to meet the demands of a simpler situation that would not be true under more demanding circumstances.

THERAPEUTIC ASPECTS

Although cannabis has been used for over 3,000 years as a medicinal herb in native and scientific medicine, its use in Western medicine sharply declined in modern times. By the 1930s, American medicine had largely supplanted cannabis with more convenient and more stable pharmaceutical preparations. Our relatively recent concern with marihuana as a drug of abuse has led to scientific investigation into its properties by means of modern pharmacological techniques. Synthesized constituents of the natural material have been produced enabling researchers to study the properties and effects of each of the components of this complex material. This recent study has reawakened scientific interest in possible therapeutic uses for the natural material or its synthesized ingredients.

Although some of marihuana's properties -- notably its psychoactivity and its tendency to accelerate heart rate -- are undesirable for most medicinal purposes, cannabis has one highly desirable property. Compared to most pharmaceuticals it is very low in biological toxicity. Indeed, it is questionable whether any deaths can be directly attributed to an overdose of marihuana or hashish.

Whether or not cannabis or perhaps some modified constituent again becomes useful in medical practice will depend on whether some of the drug's promising therapeutic properties prove to be sufficiently persistent and its side effects controllable. Marihuana's usefulness as a medication for chronic disorders may also prove to be limited by the development of tolerance to its therapeutic effects.

The most promising therapeutic applications of the drug are in the treatment of glaucoma, as an anti-emetic for cancer patients receiving chemotherapy and possibly in the treatment of

asthmatics. Other applications as a sedative-hypnotic, an anticonvulsant, an antidepressant, an analgesic and in connection with the treatment of alcoholics have been attempted, but the results have either been inconsistent or highly preliminary.

The use of cannabis and THC in treating the elevated intraocular pressures in glaucoma patients arose from the observation in normals that internal eye pressures were reduced by the drug. Subsequent research with patients has confirmed that the effect is also produced in the diseased eye and is as great as that produced by more traditional medications. Topical preparations applied to the eyes of rabbits have successfully reduced pressure raising the possibility of using such a preparation with humans. Human experimentation is not, however, expected in the immediate future because of the formidable problems in making certain that such a preparation is safe and can meet regulatory requirements (9-12, 25, 26).

The use of THC as an anti-emetic with cancer patients receiving chemotherapy shows unusual promise. One of the undesirable side effects of chemotherapeutic agents administered to cancer patients is that they produce marked nausea and vomiting. This side effect is very difficult for patients to tolerate and is also debilitating. Standard anti-emetic drugs have not, unfortunately, been notably successful in reducing this side effect. THC, by contrast, was found in a recent double-blind study (neither patient nor physician knew whether the drug received was active or inert) to be effective in virtually all of the patients receiving it. While 13 of the 16 patients receiving the drug became "high" and one third developed drowsiness, these effects were viewed as minor compared to the therapeutic benefit achieved (9-58).

Use of THC in the treatment of asthmatics is predicated on the observation that it dilates pulmonary air passages and decreases airway resistance (9-64). Based on observations in normals, research with asthmatics has demonstrated that marihuana relieves bronchospasm and has a more persistent action than traditional medication (9-65). Since smoked marihuana has obvious lung irritant properties, more recent research has employed aerosolized THC, also with promising results (9-46).

There has been a growing awareness that constituents other than delta-9-THC may have valuable therapeutic properties if freed of some of the undesirable side effects noted with THC. It is also possible for the organic chemist to produce a very wide range of chemical compounds which are broadly based on the chemical structure of the cannabinoids, but with changes in that structure which can markedly alter their action. Such chemically more remote compounds may ultimately prove more useful therapeutically than either the natural material itself or its synthesized ingredients. Because they are not the parent compounds they must, of course, be carefully tested for toxicity and therapeutic properties like any other new compound.

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